REMARKS

I. Preliminary Comments

Independent claim 70 has been amended to incorporate the DNA contamination limitation of claim 1 of its parent application which issued as Zhang, US 6,726,907 and which is set out below:

> 1. A purified adenovirus composition, the composition having a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus.

Claim 70 has also been amended to recite in the alternative the limitation from claim 78 (now canceled) that the purified adenovirus composition has a level of BSA that is below the detection level of a Western blot assay. Such a method is nowhere disclosed by the art and it would not have been obvious that a purified adenovirus composition could have been produced with such undetectable levels of BSA.

New claim 129 has been introduced which depends from claim 70 and specifies that the method provides a pharmaceutically acceptable purified adenovirus composition having (a) a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus.

New claim 130 has been introduced which recites that the purified adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml.

New claims 131 and 132 have been introduced to correspond to further refined purity levels and correspond to issued claims 9 and 16 in parent Zhang, US 6,726,907. The language of these amendments was accepted in the parent Patent, is supported at pages 92, 93 and 97 of the specification and does not enter new matter into the application.

Claims 88-90 have been amended in accordance with the suggestion of the Examiner to recite that "the adenovirus in said purified adenovirus composition is a replication

incompetent..." Finally, claim 91 has been amended in accordance with the suggestion of the Examiner to depend from claim 88. These amendments correct obvious errors in the claims and do not introduce new matter.

New claims 133-162 have been added which correspond to amended claims 71-72, 74-77, 79-98 and 129-132 but which are restricted to the embodiment wherein the purified adenovirus composition has a level of BSA that is below the detection level of a Western blot assay.

II. Outstanding Rejections

Claims 88-91 stand rejected under 35 U.S.C. §112 (second paragraph) as being indefinite.

Claims 70, 72, 75-77, and 80-97 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Shabram et al., U.S. Patent 5,837,520 (in view of Perrin et al., (Vaccine 13(13):1244-1250, 1995) Garnier et al., (Cytotechnology 15:145-155, 1994), and/or Nadeau et al., (Biotechnology and Bioengineering 51:613-623, 1996)

Claims 78 and 79 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Shabram in view of Perrin et al, Garnier et al. and/or Nadeau et al. and further in combination with Morris et al., (Williamsburg BioProcessing Conference, Nov. 18-21, 1996) or Gilbert (Williamsburg BioProcessing Conference, Nov. 18-21, 1996).

Claim 79 (sic 77) is objected to as being a duplicate of claim 75.

III. Patentability Arguments

The claims as amended above should be allowed in light of the foregoing amendments and for the reasons set out below.

A. The Indefiniteness Rejections of Claims 88-91 Under 35 U.S.C. §112 (second paragraph) Should be Withdrawn.

The indefiniteness rejections of claims 88-90 should be withdrawn in light of the amendment of the claims to recite the language suggested by the Examiner "...wherein the adenovirus in said adenovirus composition is a replication-incompetent...".

The indefiniteness rejection of claim 91 should also be withdrawn in light of the amendment suggested by the Examiner to have that claim depend from claim 88.

B. The Rejection of Claims 70, 72, 75-77 and 80-97 Under 35 U.S.C. §103(a) Over Shabram et al. US 5,837,520 In View of Perrin, Garnier and/or Nadeau Should be Withdrawn.

The rejection of claims 70, 72, 75-77 and 80-97 under 35 U.S.C. §103(a) over Shabram et al. US 5,837,520 in view of Perrin, Garnier and/or Nadeau should be withdrawn in light of the amendment of independent claim 70 to incorporate the DNA contamination limitation of claim 1 of Zhang, US 6,726,907:

> 1. A purified adenovirus composition, the composition having a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus.

It is submitted that this language addresses the issues raised by the Examiner in her Action and makes the amount of contaminating DNA in the claims comparable to that of US 6,726,907. There is nothing in any of Shabram, Perrin, Garnier or Nadeau that teaches the reduction of contaminating nucleic acid levels to the levels now claimed or suggests that the methods of the claims would achieve those levels.

More specifically, the Perrin reference relates to a rabies virus system quite distinct from adenovirus. The fact that Perrin teaches perfusion in the context of rabies virus production would in no way motivate the use of perfusion in the context of adenovirus

production. The reason for this is that rabies virus is an enveloped "budding" RNA-based rhabdovirus whereas adenovirus is a DNA capsid based non-enveloped virus of an entirely different viral family - these viruses infect and grow differently and indeed replicate differently. Moreover, adenovirus is a very fragile virus as compared to viruses like rabies virus and one would not expect that it could be handled in anywhere near the same manner as rabies virus. Therefore, there would be no *a priori* expectations that the optimal conditions in one system would be optimal or even functional in another system.

More importantly, Perrin says nothing about advantages in terms of ease of purification and purity that one might obtain by providing nutrients in the manner specified by the claims. This, in itself, is strong evidence of non-obviousness, and a finding that is in no way taught or suggested by Perrin.

The Nadeau reference is directed to improvements in recombinant protein production and not to producing adenoviral particles. Thus, it fails to teach or suggest that perfusion or other culture methods that involve exchange of media can provide a more readily purifiable adenovirus product. Nadeau does experiments with maintaining glucose levels within certain defined ranges for the purposes of improving recombinant protein production, but this is unrelated to Applicants' invention which concerns producing recombinant adenovirus itself. Applicants' claims are indeed not related in any way to recombinant protein production.

Similarly, the Garnier reference is directed to improvements in recombinant protein production and not to producing adenoviral particles. Moreover, Garnier does not appear to teach or suggest that providing nutrients to host cells by perfusion or other culture methods involving exchange of media would provide particular advantages in the production of highly purified adenovirus.

It is also the case that the secondary references teach away from Applicants' invention because they are directed to production of protein products and not toward reproduction of virus particles. Specifically, those of skill in the art would believe that the dedication of nutritional resources and energy toward protein production would detract from the production of adenoviral particles and that the recommendations of the secondary references would not be adopted by one trying to improve viral particle production.

In the absence of some suggestion in the references that Applicants' method would reduce BSA to levels below the detection level of a Western blot assay or achieve contaminating nucleic acid concentrations of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus, the rejection under the combination of those references should be withdrawn.

C. The Rejection of Claims 78 and 79 Under 35 U.S.C. §103(a) Over Shabram, In View Of Perrin, Garnier and/or Nadeau and Further In View of Morris or Gilbert Should be Withdrawn.

The rejection of 78 (now canceled in light of the incorporation of its language into claim 70) and 79 depending from claim 70 should also be withdrawn because Shabram, Perrin, Garnier and Nadeau individually and collectively fail to teach the aspect of claim 78 wherein the purified adenovirus composition has a level of BSA that is below the detection level of a Western Blot assay. While Morris and Gilbert might disclose the production of adenovirus in cells adapted to serum-free media they do not suggest that doing so according to the practice of Applicants' invention would yield a pharmaceutically acceptable purified adenovirus composition with improved purity having a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus. Accordingly, the rejection of claim 79 should be withdrawn and no similar rejection should be made against amended claim 70.

D. The Objection to Claim 79 (sic 77) Should be Withdrawn.

The objection to claim 79 (sic 77) as being a duplicate of claim 75 may now be withdrawn in light of the amendment to claim 70, from which both claims depend, to delete the recitation in that claim of "less than 0.8 ng/ml." As a result of this amendment claims 75 and 77 are no longer identical.

CONCLUSION

In view of the above amendments and for the reasons set out, Applicants believe that each of claims 70-72, 74-77, 79-98, and 129-191 are in condition for allowance. Should the Examiner wish to discuss any issue of form or substance she is encouraged to contact the undersigned attorney at the number listed below.

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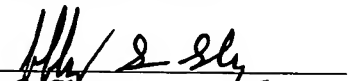
Respectfully submitted,

By 

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